6. (Amended) The [conjugate] homoconjugate of claim 1, wherein the [conjugate] homoconjugate comprises a monoclonal antibody that [asserts] has substantially no anti-neoplastic activity in an unconjugated form.

7. (Amended) The [conjugate] homoconjugate of claim 1, [wherein the antibodies are conjugated via hypercrosslinking] further defined as a homodimer.

9. (Amended) The [conjugate] homoconjugate of claim [1] 8, wherein the IgG is a mammalian IgG.

11. (Amended) A method of making a [conjugate] homoconjugate of two or more monoclonal antibodies, wherein the [conjugate] homoconjugate comprises a monoclonal antibody that does not comprise an Fc region, comprising:

obtaining a first monoclonal antibody that does not comprise an Fc region;

obtaining a second monoclonal antibody; and

conjugating the first monoclonal antibody to the second monoclonal antibody.

13. (Amended) The method of claim 11, wherein the first monoclonal antibody is a monoclonal antibody that [asserts] has anti-neoplastic activity in a conjugated form.

14. (Amended) The method of claim 11, wherein the second monoclonal antibody is a monoclonal antibody that [asserts] has anti-neoplastic activity in a conjugated form.

15. (Amended) The method of claim 11, wherein both the first monoclonal antibody and the second monoclonal antibody are [a] monoclonal antibodies that [assert] have anti-neoplastic activity in a conjugated form.

16. (Amended) The method of claim 14, wherein the [second] monoclonal antibody is an anti-CD19, anti-CD20, anti-CD21, anti-CD22, anti-breast tumor, anti-ovarian tumor, anti-prostate tumor, anti-lung tumor, or anti-αHer2 monoclonal antibody.

17. (Amended) The method of claim 14, wherein the [second] monoclonal antibody is an anti-Her2 monoclonal antibody.

18. (Amended) The method of claim 11, wherein the first monoclonal antibody is a monoclonal antibody that [asserts] has substantially no anti-neoplastic activity in an unconjugated form.

19. (Amended) The method of claim 11, wherein the second monoclonal antibody is a monoclonal antibody that [asserts] has substantially no anti-neoplastic activity in an unconjugated form.

20. (Amended) The method of claim 11, wherein both the first monoclonal antibody and the second monoclonal antibody are monoclonal antibodies that [assert] have substantially no anti-neoplastic activity in an unconjugated form.

21. (Amended) The method of claim 11, wherein the [antibodies are conjugated via hypercrosslinking] homoconjugate is further defined as a homodimer .

45. (Amended) The pharmaceutical composition of claim 43, wherein the [conjugate] homoconjugate comprises a monoclonal antibody that [asserts] has anti-neoplastic activity in a conjugated form.

48. (Amended) The pharmaceutical composition of claim 43, wherein the monoclonal antibody is a monoclonal antibody that [asserts] has substantially no anti-neoplastic activity in an unconjugated form.

49. (Amended) The pharmaceutical composition of claim 43, wherein the [antibodies are conjugated via hypercrosslinking] homoconjugate is further defined as a homodimer.

II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 1-52 were filed in the instant application. In a response to a restriction requirement, Applicants elected to cancel claims 26-42 without traverse. Claims 10, 24, and 52 are canceled herein without prejudice or disclaimer. Claims 1-9, 11-23, 25, 43-45, and 48-51 are amended herein. Support for the amended claims is found within the specification. Therefore, claims 1-9, 11-23, 25, and 43-51 are presented for reconsideration. For the convenience of the Examiner, attached as Appendix A is a list of the claims as they appear after entry of the amendments contained herein.

B. The Application Now Claims a July 8, 1997, Priority Date

The specification has been amended at page 2, line 5, to recite the priority data. A new Inventors Declaration is being submitted concurrently herewith to confirm this claim to priority. A copy of the Inventors Declaration is attached hereto as Appendix B.

C. The Claimed Invention

The Applicants' claimed invention describes homoconjugates of monoclonal antibodies which arrest cell growth and/or signal apoptosis in the targeted antigen producing tumor cells.

As used herein, "homoconjugate" refers to a conjugate comprised of monomeric antibodies, which bind to the same epitope. Homoconjugates according to the invention may be formed of monomeric antibodies that are identical, or they may, in some cases, be formed of monomeric antibodies that are not identical but bind to the same epitope. For example, a dimer of an first monomeric antibody that binds a specific CD19 epitope and lacks an Fc region conjugated to a second monomeric antibody that binds the same CD19 epitope but has an Fc region would be a homoconjugate within the terms of the invention.

There are two terms that need to be distinguished in regard to the present invention. "Conjugation" means the attachment of two or more monomeric antibodies through genetic engineering methods, chemical methods, or a combination of both. Such methods are described in the specification. By contrast, "hypercrosslinking" is what occurs when one of the homoconjugates of the invention links molecules on a target cell surface.

D. The Rejections Under 35 U.S.C. § 112, Second Paragraph, Are Overcome

The Action has rejected claims 3-7, 13-21, 45, and 48-49 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The standard for definiteness of a claim under 35 U.S.C. § 112, second paragraph, is whether a person of skill in the art can determine the scope of the invention based on the language of the claims with a "reasonable degree of certainty." MPEP § 2173.02 (citing *In re Wiggins*, 488 F.2d 538, 179 U.S.P.Q. 421 (C.C.P.A. 1973)).

Specifically, claims 3-6, 13-20, 45, and 48 are stated by the Action to be unclear in the recitation of an antibody which "asserts"... anti-neoplastic activity. In response, the Applicants respectfully note that claims 3-6, 13-20, 45 and 48 have been clarified in the amendment submitted herein to recite, "a monoclonal antibody has anti-neoplastic activity" or "has substantially no anti-neoplastic activity." It is believed that these claims are clear. One of skill in the art would be able to determine the scope of the Applicants' claimed invention based on the word "has" as it relates to "a monoclonal antibody has anti-neoplastic activity" in the specification at pg. 16, lines 10-11.

Claims 6, 18-20, and 48 are stated by the Action to be unclear in the recitation of "substantially no" anti-neoplastic activity. Claims 6, 18-20, and 48 are clear in view of the specification at pg. 11, lines 5-8. This portion of the specification recites "substantially no" anti-neoplastic activity "is that any activity detected, as measured by ^{3}H-thymidine inhibition as described herein, is not statistically significant (as determined, for example, by the Student t test) when compared to a control." One of skill in the art would be able to determine the scope of the Applicants' claimed invention based on the specification's definition of "substantially no."

Claims 7, 21, and 49 are stated by the Action to be unclear in the recitation of "hypercrosslinking." Claims 7, 21, and 49 have been amended in the Amendment submitted herewith.

Finally, the Action states that claim 9 is improper because the recitation of "the IgG" lacks antecedent basis. Claim 9 has been amended to include an antecedent basis for "IgG."

Applicants assert that the clarification of claims 3-7, 13-21, 45, and 48-49 is sufficient for a person of skill in the art to determine the scope of Applicants' claimed invention based on the claims within a reasonable degree of certainty. Accordingly, Applicants respectfully request that the rejection of claims 3-7, 9, 13-21, 45, and 48-49 under 35 U.S.C. § 112, second paragraph, be withdrawn.

E. The Rejections Under 35 U.S.C. § 102(b) Are Overcome

1. Applicable Law to Response to Office Action Dated February 14, 2000

The applicable law for a rejection of a claim under 35 U.S.C. § 102(b) has been stated by the Federal Circuit as, "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegall Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631; 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987); *Lewmar Marine, Inc. v. Barient, Inc*, 827 F.2d 744, 747; 3 U.S.P.Q2d 1766, 1767 (Fed. Cir. 1987); *Structural Rubber Products Company v. Park Rubber Company*, 749 F.2d 707, 715; 223 U.S.P.Q. 1264, 1270 (Fed. Cir. 1984). Therefore, every element of a claim must be described in the prior art reference, otherwise, the reference does not anticipate the claim under 35 U.S.C. § 102(b).

2. The Rejection over Ahlem *et al.* Is Overcome

The Action has rejected claims 1-6, 10-20, 24-25, 43-48, and 52 as being anticipated by Ahlem *et al.* Specifically, the Action contends that "Ahlem *et al.* teaches a conjugate of two, three, or more monoclonal antibodies wherein none of the monoclonal antibodies comprise an Fc region" and that "Ahlem *et al.* teaches homo and heteroconjugates." The Action also states that "Ahlem *et al.* also teaches a method of making any of the aforementioned conjugates." Finally, the Action contends that Ahlem *et al.* also teaches a conjugate comprising of a pharmaceutically acceptable carrier comprising of a **homoconjugate** or **heteroconjugate**.

Applicants respectfully disagree with the rejection of claims 1-6, 11-20, 25, and 43-48. Applicants note that present claims 1, 11, and 43 are directed to "a **homoconjugate** of two or more monoclonal antibodies, wherein the **homoconjugate** comprises a monoclonal antibody that does not comprise an Fc region," "a method of making a **homoconjugate** of two or more monoclonal antibodies, wherein the **homoconjugate** comprises a monoclonal antibody that does not comprise an Fc region...," and "a pharmaceutical composition comprising a **homoconjugate** comprising a monoclonal antibody and a pharmaceutically acceptable carrier," respectively.

Ahlem *et al.* describes "a trifunctional antibody-like compound" where the "elements of Fab_1, Fab_2, and Fab_3 of Formula I are individual Fab-like fragments wherein two of the fragments may have the same antigenic specificity, but preferably, wherein each fragment has a unique antigenic specificity relative to the others." See col. 2, lns. 35-54; col.6, lns. 45-49; and col. 7, lns. 43-55. Since all conjugates in Ahlem *et al.* have at least two different antigenic specificities, all conjugates in Ahlem *et al.* are **heteroconjugates**. In fact, Ahlem *et al.* teaches

nothing, expressly or inherently, about **homoconjugate** antibody structures, and more specifically, about the **homoconjugates** in claims 1-6, 11-20, 25, and 43-48.

Also, claims 1, 3-6, 11, 13-20, 25, 43, and 45-48 of Applicants' claimed invention claim "a homoconjugate of two or more monoclonal antibodies, wherein the homoconjugate comprises a monoclonal antibody that does not comprise an Fc region." Therefore, the homoconjugates in claims 1, 3-6, 11, 13-20, 25, 43, and 45-48 comprise at least one monoclonal antibody that does comprise an Fc region. In Ahlem *et al.*, no monoclonal antibody comprised in the heteroconjugate comprises an Fc region.

Since the Ahlem *et al.* reference lacks at least one aspect of claims 1-6, 11-20, 25, and 43-48, it cannot anticipate the aforementioned claims. Accordingly, Applicants respectfully request that the rejection of claims 1-6, 11-12, 15, 20, 25, and 43-48 under 35 U.S.C. § 102(b) be withdrawn.

3. The Rejection over Hudson Is Overcome

Claims 1-6 have been rejected by the Action as anticipated by Hudson. The correct cite to Hudson is: Hudson, "Recombinant antibody constructs in cancer therapy," Bio/Technology, 11:548-557, 1999. Attached as Appendix C is a copy of the Hudson reference. Applicants filed their patent application on July 8, 1998, and claim priority to a patent application filed or printed publication published on or after July 8, 1997, as set forth in the amendments contained herein. Since Hudson was published in 1999, which is after the priority date of Applicants' application, Hudson cannot be considered a proper prior art reference. Accordingly, Applicants respectfully request that the rejections of claims 1-6 under 35 U.S.C. § 102(b) be withdrawn.

4. The Rejection over Glennie is Overcome

The Action has rejected claims 1-3, 6, 8-9, 11-15, 18-20, 22-23, 25, 43-45, 48, and 50-51 as being anticipated by Glennie. Applicants respectfully disagree with the rejection of claims 1-3, 6, 8-9, 11-15, 18-20, 22-23, 25, 43-45, 48, and 50-51.

Glennie describes "trimeric and tetrameric" antibodies which are "bispecific and trispecific." See Abstract. Since all conjugates in Glennie have at least two distinct antigenic specificities, all conjugates in Glennie are **heteroconjugates**. Glennie teaches nothing, expressly or inherently, about **homoconjugate** antibody structures, and more specifically, about the **homoconjugates** in claims 1-3, 6, 8-9, 11-15, 18-20, 22-23, 25, 43-45, 48, and 50-51.

Also, the homoconjugates in claims 1, 3, 6, 8-9, 11, 13-15, 18-20, 22-23, 25, 43, 45, 48, and 50-51 comprise at least one monoclonal antibody that does comprise an Fc region. In Glennie, no monoclonal antibody comprised in the heteroconjugate comprises an Fc region.

Since the Glennie reference lacks at least one aspect of claims 1-3, 6, 8-9, 11-15, 18-20, and 22-23, 25, 43-45, 48, and 50-51, it cannot anticipate the aforementioned claims. Accordingly, Applicants request that the rejection of claims 1-3, 6, 8-9, 11-15, 18-20, 22-23, 25, 43-45, 48, and 50-51 under 35 U.S.C. § 102(b) be withdrawn.

5. The Rejection over Ghetie *et al.* is Overcome

The Action has rejected claims 1-3 and 6 as being anticipated by Ghetie *et al.* Applicants respectfully disagree with the rejection of claims 1-3 and 6.

Ghetie *et al.* purports to describe a conjugate comprising of "two Fv regions with different specificities." See pg. 314. Since there are two distinct antigenic specificities in the Ghetie *et al.* conjugates, all conjugates in Ghetie *et al.* are **heteroconjugates**. In fact, Ghetie

et al. teaches nothing, expressly or inherently, about **homoconjugate** antibody structures, and more specifically, about the **homoconjugates** in claims 1-3 and 6.

Furthermore, claims 1, 3, and 6 comprise at least one monoclonal antibody that does comprise an Fc region. In Ghetie, no monoclonal antibody comprised in the heteroconjugate comprises an Fc region.

Since the Ghetie *et al.* reference lacks at least one aspect of claims 1-3 and 6, it cannot anticipate the aforementioned claims. Accordingly, Applicants request that the rejection of claims 1-3 and 6 under 35 U.S.C. § 102(b) be withdrawn.

6. The Rejection over Bosslet *et al.* is Overcome

The Action has rejected claims 1-3 and 6 as being anticipated by Bosslet *et al.* Applicants respectfully disagree with the rejection of claims 1-3 and 6.

Bosslet *et al.* purports to describe a conjugate that is bi-specific and oligospecific for antigens. *See* col. 1, lns. 10-14. Since all conjugates in Bosslet *et al.* have at least two distinct antigenic specificities, all conjugates in Bosslet *et al.* are **heteroconjugates**. In fact, Bosslet *et al.* teaches nothing, expressly or inherently, about **homoconjugate** antibody structures, and more specifically, about the **homoconjugates** in claims 1-3 and 6.

Furthermore, claims 1, 3, and 6 comprise at least one monoclonal antibody that does comprise an Fc region. In Bosslet *et al.*, no monoclonal antibody comprised in the heteroconjugate comprises an Fc region.

Since the reference lacks at least one aspect of claims 1-3 and 6, it cannot anticipate the aforementioned claims. Accordingly, Applicants request that the rejection of claims 1-3, and 6 under 35 U.S.C. § 102(b) be withdrawn.

7. The Rejection over Cumber *et al.* is Overcome

The Action has rejected claims 1-2, 6, 10-12, 18-20, and 23-24 as being anticipated by Cumber *et al.* Applicants respectfully disagree with the rejection of claims 1-2, 6, 10-12, 18-20, and 23-24.

Claims 1, 6, 11, 18-20, and 23 comprise at least one monoclonal antibody that does comprise an Fc region. Cumber *et al.* purports to describe a bivalent conjugate consisting of two FvCys fragments. *See* Abstract. Since the Cumber *et al.* conjugate is comprised of Fv fragments, the conjugate does not comprise an antibody comprising an Fc region. In fact, Cumber *et al.* does not expressly or inherently describe a homoconjugate that comprises at least one monoclonal antibody that comprises an Fc region.

The homoconjugates in claims 1-2, 6, 11-12, 18-20, and 23 do not contain cysteine residues. Cumber *et al.* appears to teach a bivalent bisFvCys conjugate and a method to make such conjugate. *See* pg. 125, lns. 2-4. Cumber *et al.* also does not expressly or inherently anticipate a homoconjugate comprising monoclonal antibodies that do not comprise cysteine residues.

Because the Cumber *et al.* reference lacks at least one aspect of claims 1-2, 6, 11-12, 18-20, and 23, it cannot anticipate the aforementioned claims. Accordingly, Applicants request that the rejection of claims 1-2, 6, 11-12, 18-20, and 23 under 35 U.S.C. § 102(b) be withdrawn.

8. The Rejection Over Bagshawe *et al.* is Overcome

Claims 1, 3, 9, 11, 13, and 23 have been rejected by the Action as being anticipated by Bagshawe *et al.* Applicants filed their patent application on July 8, 1998, and claim priority to a

patent application filed on or after July 8, 1997, as set forth in the amendments contained herein. Since the Bagshawe *et al.* patent was issued on November 4, 1997, which is after the priority date of Applicants' application, Bagshawe *et al.* cannot be considered a proper prior art reference. Accordingly, Applicants respectfully request that the rejections of claims 1, 3, 9, 11, 13, and 23 under 35 U.S.C. § 102(b) be withdrawn.

F. The Rejections Under 35 U.S.C. § 103 Are Overcome

1. Applicable Law to Response to Office Action Dated February 14, 2000

To render a claim as *prima facia* obvious under 35 U.S.C. § 103, the prior art reference must:

(1) suggest to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and

(2) reveal that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success.

In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991) *citing In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). Furthermore, "both the suggestion and the reasonable expectation of success must be founded in the prior art, not in applicant's disclosure." MPEP § 2143 (citing *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991)). Therefore, if either part of the above test for obviousness is not met, the claim cannot be considered *prima facia* obvious under 35 U.S.C. § 103.

Also, to rely on a reference under 35 U.S.C. § 103, the reference must be analogous prior art. The MPEP defines "analogous art" by stating, "in order to rely on a reference as a basis for rejection of an applicant's invention, the reference must be in the field of applicant's endeavor

or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned." MPEP § 2141.01(a) (*citing In re Oetiker, 977 F.2d 1443*, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992).

Finally, when combining prior art references to establish obviousness, the MPEP states that "the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." MPEP § 2143.01 citing *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). Therefore, if the prior art references do not suggest the desirability to combine the references, then the combination of references fails to establish a *prima facia* case of obviousness under 35 U.S.C. § 103.

2. The Rejection Over Ahlem *et al.* in view of Marches *et al.* or Racila *et al* is Overcome

The Action has rejected claims 1-7, 10-21, 24-25, 43-49, and 52 under 35 U.S.C. § 103 as being unpatentable over Ahlem *et al.*, in view of Marches *et al.* or Racila *et al.* Specifically, the Action contends that Ahlem *et al.* "teaches as applied to claims 1-6, 10-20, 24-25, 43-48, and 52" but "fails to teach hypercrosslinking to make the antibody conjugates." The Action also states that Marches *et al.* teaches hypercrosslinking increases apoptosis and cell cycle arrest and Racila *et al.* teaches hypercrosslinking increases apoptosis. Finally, the Action asserts that Ahlem *et al.* combined with Marches *et al.* or Racila *et al.* teaches claims 7, 21, and 49. Thus, the Action asserts that claims 1-7, 10-21, 24-25, 43-49, and 52 are *prima facia* obvious over the prior art.

Applicants respectfully disagree with the rejection of claims 1-7, 11-21, 25, and 43-49. Applicants note that present claims 1, 11, and 43, are directed to "a homoconjugate of two or

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more monoclonal antibodies, wherein the homoconjugate comprises a monoclonal antibody that does not comprise an Fc region," "a method of making a homoconjugate of two or more monoclonal antibodies, wherein the homoconjugate comprises a monoclonal antibody that does not comprise an Fc region...," and "a pharmaceutical composition comprising a homoconjugate comprising a monoclonal antibody and a pharmaceutically acceptable carrier," respectively.

The present reference relied upon by the Action to render claims 1-6, 11-20, 24-25, and 43-48 as *prima facia* obvious clearly fails to satisfy the *In re Vaeck* test for obviousness as set forth above.

Applicants' claimed **homoconjugates** rely on their single antigenic specificity in order to cause the target cell to undergo cell cycle arrest (hereinafter "CCA") and/or apoptosis. The binding and hypercrosslinking of cell surface antigens to the **homoconjugate** elicits a negative signal, thus sending the target cell into CCA and/or apoptosis. Ahlem *et al.* appears to teach a **heteroconjugate** where the conjugate has specificity for an antigen producing target cell and a therapeutic agent to the target cell, or where the conjugate has specificity for a target cell and a receptor/receptor complex and accessory molecule on the surface of a T-cell. *See* Abstract; col. 3, lns. 61-68; col. 4, lns. 1-10. The **heteroconjugate** in Ahlem *et al.* relies on its bispecificity or trispecificity to bring about its desired effect on the target cell. Therefore, Ahlem *et al.* does not suggest to those of ordinary skill in the art that they should make "a **homoconjugate** of two or more monoclonal antibodies, wherein the **homoconjugate** comprises a monoclonal antibody that does not comprise an Fc region."

Furthermore, in view of Ahlem *et al.*, those of ordinary skill would not have a reasonable expectation of success that a **homoconjugate** of two or more monoclonal antibodies, wherein the **homoconjugate** comprises a monoclonal antibody that does not does not comprise an Fc region,

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would cause the antigen producing target cell to undergo CCA and/or apoptosis. Again, Ahlem *et al.* appears to use its conjugate as a carrier molecule for a therapeutic agent or as a bridge between an antigen producing target cell and a T-cell, while Applicants' **homoconjugate** relies on its single antigenic specificity to bring about CCA and or apoptosis.

Also, the Ahlem *et al.* reference cannot be considered analagous prior art to Applicants' claimed invention. One of ordinary skill in the art of would not rely on Ahlem *et al.* to produce a homoconjugate that directly causes the target cell to undergo CCA and/or apoptosis. In fact, *Ahlem et al.* only teaches an effective way to transport a therapeutic agent or imaging agent to a target cell. Therefore, Ahlem *et al.* cannot be considered analagous art to Applicants' claimed invention.

Rejected claims 7, 21, and 49 relate specifically to homodimers or their use. The claims, prior to the clarifying amendments submitted herewith 7, 21, and 49 are rejected over Ahlem *et al.* in view of Marches *et al.* or Racila *et al.* This combination of references fails to establish a *prima facia* case of obviousness to substantiate the rejection of these claims under 35 U.S.C. § 103. As stated above, claims 1-6, 11-20, 25, and 43-48 are not obvious in view of Ahlem *et al.* Furthermore, claims 7, 21, and 49 are dependent claims of claims 1, 11, and 43 respectively. Therefore claims 7, 21, and 49 cannot be considered *prima facia* obvious under 35 U.S.C. § 103 by combining Ahlem *et al.* with Marches *et al.* or Racila *et al.*

Also, no motivation exists to combine Ahlem *et al.* with Marches *et al.* or Racila *et al.* to result in the claimed homodimers. Ahlem *et al.* suggests nothing about the desirability of combining itself with Marches *et al.* or Racila *et al.* In fact, the Action acknowledges that Ahlem *et al.* fails to teach the making of antibody conjugates. Marches *et al.* and Racila *et al.*, do not report the use of homoconjugates of two or more monoclonal antibodies. Rather,

Marches *et al.* and Racila *et al.* used a second layer of antibody to crosslink antibodies already bound to the cell surface antigens. This induced a negative signal, thereby sending the cell into apoptosis and/or CCA. Therefore, there is no express or inherent suggestion in Marches *et al.* or Racila *et al.* to make homodimers as seen in claims 7, 21, and 49, or to make heteroconjugates as seen in Ahlem *et al.*

Since the Ahlem *et al.* reference does not satisfy either element of the *In re Vaeck* test for obviousness and cannot be considered analagous art to Applicants' claimed invention, the rejection of claims 1-6, 11-20, 25, and 43-48 by the Action for obviousness is improper. Furthermore, the combination of references cited by the Action in the rejection of claims 7, 21, and 49, fails to establish a case of *prima facia* obviousness. Accordingly, Applicants respectfully request that the rejection of claims 1-7, 11-21, 25, and 43-49 under 35 U.S.C. § 103 be withdrawn.

3. The Rejection Over Hudson In View of Marches *et al* or Racila *et al.* Is Overcome

As stated above, Hudson cannot be considered a proper prior art reference. Accordingly, Applicants respectfully request that the rejection of claims 1-7 under 35 U.S.C. § 102(b) be withdrawn.

4. The Rejection Over Glennie, In View of Marches *et al* or Racila *et al.* Is Overcome

The Action has rejected claims 1-3, 6-9, 11-15, 18-23, 25, 43-45, and 48-51 under 35 U.S.C. § 103 as being unpatentable over Glennie in view of Marches *et al.* or Racila *et al.* Applicants respectfully disagree with the rejection of claims 1-3, 6-9, 11-15, 18-23, 25, 43-45, and 48-51.

Glennie appears to teach a **heteroconjugate** where the conjugate has specificity for a target cell and is used as a carrier of a therapeutic agent to the target cell, or is used for targeting effector T-cells to the target cell. See pg. 1 lines 12 through 28. The **heteroconjugate** in Glennie relies on its bispecificity to bring about its desired effect on the target cell. Therefore, Glennie does not suggest to those of ordinary skill in the art that they should make "a **homoconjugate** of two or more monoclonal antibodies, wherein the conjugate comprises a monoclonal antibody that does not comprise an Fc region."

Furthermore, in view of Glennie, those of ordinary skill would not have a reasonable expectation of success that a homoconjugate of two or more monoclonal antibodies comprising a monoclonal antibody that does not does not comprise an Fc region would cause the antigen producing target cell to undergo CCA and/or apoptosis.

Also, Glennie cannot be considered an analagous art reference because one of ordinary skill in the art would not rely on Glennie to produce a homoconjugate that directly causes the target cell to undergo CCA and/or apoptosis.

The Action has also rejected Claims 7, 21, and 49 over Glennie in view of Marches *et al.* or Racila *et al.* As stated above, Glennie does not teach the independent claims 1, 11, and 49. Therefore, claims 7, 21, and 49 cannot be considered *prima facia* obvious under 35 U.S.C. § 103.

Furthermore, no motivation exists to combine Glennie with Marches *et al.* or Racila *et al.* Glennie suggests nothing about the desirability of combining it with Marches *et al.* or Racila *et al.* Also, there is no express or inherent suggestion in Marches *et al.* or Racila *et al.* to conjugate monoclonal antibodies.

Since Glennie does not satisfy either element of the *In re Vaeck* test for obviousness and cannot be considered analagous art to Applicants' claimed invention, the rejection of claims 1-3,

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6, 8-9, 11-15, 18-20, 22-23, 25, 43-45, 48, and 50-51 by the Action for obviousness is improper. Furthermore, as stated above, the combination of references cited by the Action in the rejection of claims 7, 21, and 49, fails to establish a *prima facia* case of obviousness. Accordingly, Applicants respectfully request that the rejection of claims 1-3, 6-7, 8-9, 11-15, 18-21, 22-23, 25, 43-45, 48-49, and 50-51 under 35 U.S.C. § 103 be withdrawn.

5. The Rejection Over Ghetie *et al.*, In View of Marches *et al* or Racila *et al.* Is Overcome

The Action has rejected claims 1, 3, and 6-7 under 35 U.S.C. § 103 as being unpatentable over Ghetie *et al.* in view of Marches *et al.* or Racila *et al.* Applicants respectfully disagree with the rejection of claims 1, 3, and 6-7.

Ghetie *et al.* describes a **heteroconjugate** comprising of "two Fv regions with different specificities." See pg. 314. These conjugates in Ghetie *et al.* "promoted adhesion between human T-cells and L6 tumor cells and stimulated the T-cells to proliferate and mediate killing of L6 tumor cells." See pg. 314 through 315. The **heteroconjugate** in Ghetie requires two distinct antigenic specificities to carry out its stated purpose. Therefore, Ghetie *et al.* does not suggest to those of ordinary skill in the art that they should make "a **homoconjugate** of two or more monoclonal antibodies, wherein the conjugate comprises a monoclonal antibody that does not comprise an Fc region."

Furthermore, in view of Ghetie *et al.*, those of ordinary skill would not have a reasonable expectation of success that a homoconjugate of two or more monoclonal antibodies comprising a monoclonal antibody that does not does not comprise an Fc region would cause the antigen producing target cell to undergo CCA and/or apoptosis.

Also, Ghetie *et al.* cannot be considered an analagous art reference because one of ordinary skill in the art would not rely on Ghetie *et al.* to produce a homoconjugate that directly causes the target cell to undergo CCA and/or apoptosis.

The Action has rejected Claim 7 over Ghetie *et al.* in view of Marches *et al.* or Racila *et al.* As stated above, Ghetie *et al.* does not teach the independent claim 1. Therefore, claim 7 cannot be considered *prima facia* obvious under 35 U.S.C. § 103 by combining Ghetie *et al.* with Marches *et al.* or Racila *et al.*

Alternatively, no motivation exists to combine Ghetie *et al.* with Marches *et al.* or Racila *et al.* Ghetie *et al.* suggests nothing about the desirability of combining it with Marches *et al.* or Racila *et al.* Also, there is no express or inherent suggestion in Marches *et al.* or Racila *et al.* to conjugate monoclonal antibodies.

Since the Ghetie *et al.* reference does not satisfy either element of the *In re Vaeck* test for obviousness and cannot be considered an analagous art reference, the rejection by the Action for obviousness is improper as to claims 1, 3, and 6. Furthermore, as stated above, the combination of references cited by the Action in the rejection of claim 7 fails to establish a *prima facia* case of obviousness. Accordingly, Applicants respectfully request that the rejections of claims 1, 3, and 6-7 under 35 U.S.C. § 103 be withdrawn.

6. The Rejection Over Bosslet *et al.*, In View of Marches *et al* or Racila *et al.* Is Overcome

The Action has rejected claims 1, 3, and 6-7 under 35 U.S.C. § 103 as being unpatentable over Bosslet *et al.* in view of Marches *et al.* or Racila *et al.*

Bosslet *et al.* teaches a **heteroconjugate** comprising "F(ab) fragments of antibodies of two or more different specificities by means of suitable linkers." See Col. 1 lines 10 through 15.

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In the Bosslet *et al.* conjugates, one specificity is directed towards an antigen producing target cell, while the second specificity is for a radioactive ligand "which results in selective destruction of the target tissue..." See Col. 1, lines 66 through 67 ; Col. 2 lines 1 through 3. The **heteroconjugate** in Bosslet *et al.* requires two specficities to destroy the antigen producing target cell. Therefore, Bosslet *et al.* does not suggest to those of ordinary skill in the art that they should make "a **homoconjugate** of two or more monoclonal antibodies, wherein the conjugate comprises a monoclonal antibody that does not comprise an Fc region."

Furthermore, in view of Bosslet *et al.*, those of ordinary skill would not have a reasonable expectation of success that a homoconjugate of two or more monoclonal antibodies comprising a monoclonal antibody that does not does not comprise an Fc region would cause the antigen producing target cell to undergo CCA and/or apoptosis.

Also, Bosslet *et al.* cannot be considered an analagous art reference because one of ordinary skill in the art would not rely on Bosslet *et al.* to produce a homoconjugate that directly causes the target cell to undergo CCA and/or apoptosis.

The Action has also rejected Claim 7 over Bosslet *et al.* in view of Marches *et al.* or Racila *et al.* As stated above, Bosslet *et al.* does not teach the independent claim 1. Therefore, claim 7 cannot be considered *prima facia* obvious under 35 U.S.C. § 103 by combining Bosslet *et al.* with Marches *et al.* or Racila *et al.*

Alternatively, no motivation exists to combine Bosslet *et al.* with Marches *et al.* or Racila *et al.* Bosslet *et al.* suggests nothing about the desirability of combining it with Marches *et al.* or Racila *et al.* Also, there is no express or inherent suggestion in Marches *et al.* or Racila *et al.* to conjugate monoclonal antibodies.

Since the Bosslet *et al.* reference does not satisfy either element of the *In re Vaeck* test for obviousness and cannot be considered an analagous art reference, the rejection by the Action for obviousness is improper as to claims 1, 3, and 6. Furthermore, as stated above, the combination of references cited by the Action in the rejection of claim 7 fails to establish a *prima facia* case of obviousness. Accordingly, Applicants respectfully request that the rejections of claims 1, 3, and 6-7 under 35 U.S.C. § 103 be withdrawn.

7. The Rejection Over Cumber *et al.*, In View of Marches *et al* or Racila *et al.* Is Overcome

The Action has rejected claims 1-2, 6-7, 10-12, 18-21, and 23-24 under 35 U.S.C. § 103 as being unpatentable over Cumber *et al.* in view of Marches *et al.* or Racila *et al.* Applicants respectfully disagree with the rejection of claims 1-2, 6-7, 10-12, 18-21, and 23-24.

In Applicants' claimed invention, claims 1, 6-7, 11, 18-21, and 23 all have at least one monoclonal antibody that comprises an Fc region. Cumber *et al.* teaches a "bisFvCys conjugate by a simple crosslinking strategy." See. Pg. 124 lines 2 through 3. The purpose of creating the bisFvCys conjugate was to test the stability of it. See Abstract. Cumber *et al.* does not suggest to those of ordinary skill in the art that they should make "a homoconjugate of two or more monoclonal antibodies, wherein the homoconjugate comprises at least one monoclonal antibody comprising of an Fc region."

Furthermore, in view of Cumber *et al.*, those of ordinary skill would not have a reasonable expectation of success that Applicants' homoconjugates in claims 1-2, 6-7, 11-12, 18-21, and 23 would cause the antigen producing target cell to undergo CCA and/or apoptosis upon the homoconjugate binding to and crosslinking cell surface antigens on the target cell. Cumber

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et al. only measured the stability of a bivalent conjugate comprising only Fv regions comprising cysteine residues.

Also, Cumber *et al.* cannot be considered an analagous art reference because one of ordinary skill in the art would not rely on Cumber *et al.* to produce a homoconjugate that directly causes the target cell to undergo CCA and/or apoptosis.

Finally, the MPEP has stated, "if an independent claim is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom is nonobvious. MPEP § 2143.03 (*citing In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). Since claims 1 and 11 are not considered obvious under Cumber *et al.*, then the dependent claims, 2 and 12, are nonobvious.

The Action has rejected claims 7 an 21 over Cumber *et al.* in view of Marches *et al.* or Racila *et al.* This combination of references fails to establish a *prima facia* case of obviousness to substantiate the rejection of this claim under 35 U.S.C. § 103. As stated above, Cumber *et al.* does not teach claims 1 and 11. Therefore, claim 7 and 21 cannot be considered *prima facia* obvious under 35 U.S.C. § 103 by combining Cumber *et al.* with Marches *et al.* or Racila *et al.*

Also, no motivation exists to combine Cumber *et al.* with Marches *et al.* or Racila *et al.* Cumber *et al.* suggests nothing about the desirability of combining it with Marches *et al.* or Racila *et al.* Also, there is no express or inherent suggestion in Marches *et al.* or Racila *et al.* to conjugate monoclonal antibodies.

Since the Cumber *et al.* reference does not satisfy both elements of the *In re Vaeck* test for obviousness and since it is not an analagous reference to Applicants' claimed invention , the rejection by the Action for obviousness is improper as to claims 1-2, 6, 11-12, 18-20, and 23. Furthermore, the combination of references cited by the Action in this case fails to establish a *prima facia* case of obviousness as to claims 7 and 21. Accordingly, Applicants respectfully

request that the rejection of claims 1-2, 6-7, 11-12, 18-21, and 23 under 35 U.S.C. § 103 be withdrawn.

8. The Rejection Over Bagshawe *et al.*, Is Overcome

As stated above, Bagshawe *et al.* cannot be considered a proper prior art reference. Accordingly, Applicants respectfully request that the rejection of claims 1, 3, 7, 9, 11, 13, 21, and 23 be withdrawn.

III. REQUEST FOR EXTENSION OF TIME

Pursuant to 37 C.F.R. § 1.136(a), Applicants petition for an extension of time of two months to and including July 14, 2000, in which to respond to the Office Action dated February 14, 2000.

Pursuant to 37 C.F.R. § 1.17, a check in the amount of $190.00 is enclosed, which is the process fee for a small entity for a two-month extension of time.

If the check is inadvertently omitted, or should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to the enclosed materials, or should an overpayment be included herein, the Assistant Commissioner is authorized to deduct or credit said fees from or to Fulbright & Jaworski Deposit Account No. 50-1212/10017628/MBW.